SAGE evidence to recommendations framework[i]

Detailed evidence related to the evidence to recommendation table can be found in the background papers presented to the Strategic Advisory Group of Experts (SAGE) on Immunization in October 2017[1]

Question: Should BCG be recommended at birth, over no vaccination, to immunocompetent infants based on the evidence for BCG efficacy and effectiveness to mitigate against various forms of tuberculosis (TB)?

Population: Immunocompetent infants.
Intervention: BCG vaccination at birth.
Comparison(s): No vaccination.
Outcome: Protection against various forms of TB.

Background:
The BCG vaccine is one of the most widely used vaccines and based on previous available evidence, it prevents severe forms of tuberculosis (TB) in children, known to be most prone to disseminated TB. BCG vaccination is recommended by the WHO for all infants, as soon as possible after birth, in countries with a high burden of TB.[2] Additional TB prevention strategies include treatment of latent TB infection in HIV infected persons and chemoprophylaxis for young child contacts of adults with pulmonary TB (PTB).[3] Recent research has extensively evaluated the efficacy and effectiveness of BCG vaccine against various forms of TB (TB infection, PTB, severe disease), and this evidence is important to guide current policy and practice regarding use of BCG vaccine for the mitigation of various forms of TB."

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	The incidence of TB has fallen by an average of 1.5% per year since 2000. Decline in TB incidence is slow, falling on average by ~1.5% per year since 2000, and TB continues to be one of the top 10 causes of morbidity and mortality globally	In 2015, 87% of new TB cases occurred in the 30 high TB burden countries, however TB is reported in all regions and countries. Six countries accounted for 60% of the new TB cases: India, Indonesia, China, Nigeria, Pakistan, and South Africa.

[1] Working Group Report, BCG Working Group, available at http://www.who.int/immunization/sage/meetings/2017/october/en/, accessed September 2017.
[2] WHO BCG Position Paper. 2004. http://www.who.int/wer/2004/en/wer7904.pdf?ua=1
[3] http://www.who.int/tb/publications/ltbi_document_page/en/, accessed July 2016

						(10.4 million new cases and 1.8 million deaths in 2015), with little likelihood of achieving the SDG at current rate of decline in incidence.[4]	An estimated 25% of the global population today has latent TB infection, which poses a big challenge to the control or elimination of TB in this generation.
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Recent evidence of the additional protective effects of BCG vaccination against TB infection, progression to active TB disease, pulmonary TB and death has implications on its overall effect on the control of TB.A systematic review and meta-analysis of 18 RCTs comparing vaccinated with unvaccinated participants, provided evidence on BCG vaccine efficacy (VE) against severe forms of TB, and against PTB as follows[5]. ***Efficacy against miliary & meningeal TB (severe disseminated TB):*** Pooled VE was 85% overall (95% CI 69 – 92%); efficacy was higher with neonatal BCG (VE 90%), and for BCG given to TST negative school age children (VE 92%); VE was low in older children and adults. ***Efficacy against Pulmonary TB:***	In Mangtani et al meta-analysis of 18 RCTs, the effect of latitude on BCG efficacy/effectiveness was evaluated. Protection against PTB, efficacy appeared to be higher in settings further from the equator (latitude > 40^{o} RR 0.32, 95% CI 0.22-0.46 versus latitude 0^{o} - <20^{o} RR 0.78, 95% CI 0.58 – 1.05), however closer examination of the specific populations included in different latitudes varied by age at vaccination and by stringency of TST testing for older children and adults, as such this finding is interpreted with caution.[5] Findings of higher VE at high latitude settings may be related to inclusion of individuals who were not already mycobacteria exposed. The 5 studies from latitude 20^{o} – 40^{o} were a mixture of school age or older participants, with mixture of stringent TST testing (3

[4] WHO. http://www.who.int/mediacentre/factsheets/fs104/en/

[5] Mangtani P, Abubakar I, Ariti C, Beynon R, Pimpin L, Fine PEM, et al. Protection by BCG vaccine against tuberculosis: A systematic review of randomized controlled trials. Clin Infect Dis. 2014;58(4):470–80.

				Pooled VE for birth BCG across 5 RCTs was 59% (95% CI 42-71%) VE for BCG given to TST negative school age children across 4 RCTs was 74% (95% CI 63-82%) Protection in school age children not stringently TST tested, and in older persons with or without stringent testing protection was weaker (VE 41% and VE <20% respectively). [5] ***Prevention of Primary M.Tb infection:*** A systematic review and meta-analysis of 14 observational studies in which 3,855 child contacts (age <18 years) of adults with PTB underwent interferon gamma release assay (IGRA) to determine M.Tb infection status, and prevalence of IGRA positivity was compared among those with and without previous BCG vaccination. Prior BCG vaccination was associated with 19 – 27% lower prevalence in TB infection in the child contacts. In 6 of those studies with follow up for disease progression among those already infected (IGRA+) at	studies) and non-stringent testing (2 studies), most studies of low bias. A multivariable analysis of efficacy by latitude that included age, TST testing and diagnostic bias, did not show a statistically significant difference between 20-40 degrees (RR 1.17; 95%CI 0.58-2.36) or 0-20 degrees (RR 1.73; 95%CI 0.93-3.25), compared to >40 degrees latitude.[5]

			enrolment, BCG vaccinated children had 58% (95% CI 23-77%) less progression to any active TB compared to unvaccinated children.[6]	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐ *Un-certain* ☐ *Yes* ☒ *Varies* ☐	BCG vaccination in immunocompetent infants is considered safe.[1]	A systematic review analyzed adverse events following BCG immunization. There was substantial variation in the reported rate of lymphadenitis across countries and across periods, ranging from as low as 0.41 per 1,000 vaccinated children in Saudi Arabia in 2012 to as much as 308 per 1,000 in HIV positive vaccinated children in Haiti in 1994. There was substantial variation in the reported rate of disseminated BCG across countries and across periods, ranging from 1.81 per 1,000 in South Africa to 167 per 1,000 in France. [7]
	Balance between benefits and harms	*Favours inter-vention* ☒ *Favours com-parison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☐	BCG is safe and reduces various forms of TB in children and young adults.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☒ *Mod-erate* ☒ *High* ☐ Safety of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☒ *Mod-erate* ☒ *High* ☐	The quality of the evidence for the efficacy against TB disease was moderate. The quality evidence for the efficacy against primary TB infection was low. The evidence was low to moderate quality due to estimates from	There is a paucity of evidence comparing the effectiveness of different BCG products.

[6] Roy A, Eisenhut M, Harris RJ, Rodrigues LC, Sridhar S, Habermann S, et al. Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic review and meta-analysis. BMJ. 2014;349(aug04_5):g4643. Available http://www.bmj.com/content/349/bmj.g4643, accessed September 2017.

[7] Uthman et al. Systematic review on safety of BCG vaccination. available at http://www.who.int/immunization/sage/meetings/2017/october/en/, accessed September 2017.

		observational studies and RCTs.	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes? ☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ Probably no important uncertainty or variability ☐ No important uncertainty or variability ☐ No known undesirable outcomes	No evidence available, though it is assumed that in general, there is no important uncertainty or variability.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects? ☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies	There is no evidence on the values and preferences of the target population.	
RESOURCE USE	Are the resources required small? ☐ No ☐ Uncertain ☒ Yes ☐ Varies	BCG vaccination is part of the routine immunization programme in many countries; therefore, additional resources will not be needed.	
	Cost-effectiveness ☐ No ☐ Uncertain ☒ Yes ☐ Varies	Formal cost-effectiveness analyses have not been conducted, but given the emerging evidence of BCG vaccine protection against various forms of TB and a possibly longer duration than previously assumed, the benefits override the cost of the vaccine.	

EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐ *Un-certain* ☐ *Re-duced* ☒ *Varies* ☐	Due to protection by BCG from various forms of TB, particularly in resource-constrained settings, BCG vaccination is expected to reduce health inequities.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention* ☒ *Com-parison* ☐ *Both* ☐ *Neither* ☐ *Un-clear* ☐	Given the protection by BCG from various forms of TB, administering BCG is an acceptable option to key stakeholders, as it requires no change to the current immunization schedule.	
	Which option is acceptable to target group?	*Inter-vention* ☒ *Com-parison* ☐ *Both* ☐ *Neither* ☐ *Un-clear* ☐	Ensuring early protection of infants against various forms of TB is likely to be acceptable to the target group.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Un-certain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	BCG vaccination is part of the routine immunization programme in many countries; therefore, continuation and improvements in BCG delivery are required.	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒
Type of recommendation	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐

Recommendation (text)	• In countries or settings with a high incidence of TB and/or leprosy, a single dose of BCG vaccine should be given to neonates at birth, or as soon as possible thereafter, for prevention of TB and leprosy. If it cannot be given at birth, it should be given at the earliest opportunity thereafter and should not be delayed. Any delay in vaccination may lead to opportunities for known or unknown exposure to TB or leprosy infected contacts. • Co-administration of BCG with the hepatitis B birth dose is safe and strongly recommended. In order to avoid missed opportunities for neonatal vaccination, BCG multi-dose vials should be opened and used despite any wastage of unused vaccine. • If the birth dose was missed, catch-up vaccination of unvaccinated older infants and children is recommended since evidence shows it is beneficial. Catch-up vaccination should be done at the earliest convenient encounter with the health-care system to minimize known or unknown exposure to TB or leprosy infected contacts.
Implementation considerations	• BCG vaccination relies on the assumption of BCG availability and that it is already routinely administered as part of the national immunization programme.
Monitoring and evaluation	• Continued monitoring of BCG vaccination coverage at birth or soon after is important to ensure that infants are protected early in life.
Research priorities	• Research on the effect of latitude on BCG vaccine efficacy and effectiveness is required by conducting case-control and prospective cohort studies performed within low latitudes in particular. Prior infection or sensitisation to environmental mycobacteria is avoided if given BCG soon after birth. Studies on BCG vaccine efficacy and effectiveness should be carefully assessed when BCG is not given soon after birth or after stringent testing if given in childhood.

[i] This Evidence to Recommendation table is based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel). http://www.decide-collaboration.eu/WP5/Strategies/Framework